A CLINICAL AND EXPERIMENTAL STUDY OF THE EFFECT OF SINGLE AND DIVIDED DOSES OF RADIATION ON CATARACT PRODUCTION*

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INTRODUCTION

IN EVALUATING THE POSSIBILITY OF THE OCCURRENCE of a radiation cataract, it is necessary to know the dose and quality of radiation received. The question also arises as to whether the over-all time during which the radiation was delivered has an effect. The importance lies in the fact that it enables one to estimate the possibility of a cataract for a given therapeutic dose delivered during a particular period. With the increasing use of radiation in many fields, there is also the greater possibility of an accidental cataract for which the visual prognosis may depend not only on the dose but perhaps also on the duration of the exposure. The purpose of the present study was to determine quantitatively if possible, the effect of extending the exposure time.

In 1944 Strandqvist[1] published his now classic study on the varying effects of a given dose of ionizing radiation delivered in different time intervals. In this report he plotted the dose against the duration of treatment for a group of patients treated for squamous carcinoma of the skin, with a follow-up of five years or more. On this plot he drew two lines which encompassed a narrow zone in which recurrences and damage were equally likely to occur. This was felt to be the zone for correct dosage. Below this zone were all of the recurrences, and

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above it were all of the radiation complications, that is, the cases without recurrences but with ulceration and necrosis of the skin. The slope of the curve, which on log-log paper became a straight line, indicated the time-dose relationship for this particular tissue and effect. Essentially it indicated that smaller doses delivered in a short time interval were equivalent in effect on squamous carcinoma to larger doses delivered over a longer period of time. The curve is really an iso-effect line in that the time-dose combination defined by a given point on the line would, if given to a group of patients, produce a similar response in the same fraction of patients as any other time-dose combination on the curve, subject of course to statistical variations.[3]

The time-dose relationship has been studied for many different tissues. This work has been reviewed recently and discussed by DuSault.[2,3] These studies indicated that the slope of the time-dose curve varied for different effects and tissues. The lens is one of the few tissues that has not been so analyzed in detail. Several reports in the literature indicate a lessened effect with fractionation.[4–10] Theoretically one might expect little, if any, time-dose relationship for the lens. It has a low metabolic activity compared to many other tissues, has no blood supply, and, being enclosed in a capsule, is unable to eliminate injured cells as, for example, is done by desquamation of skin.

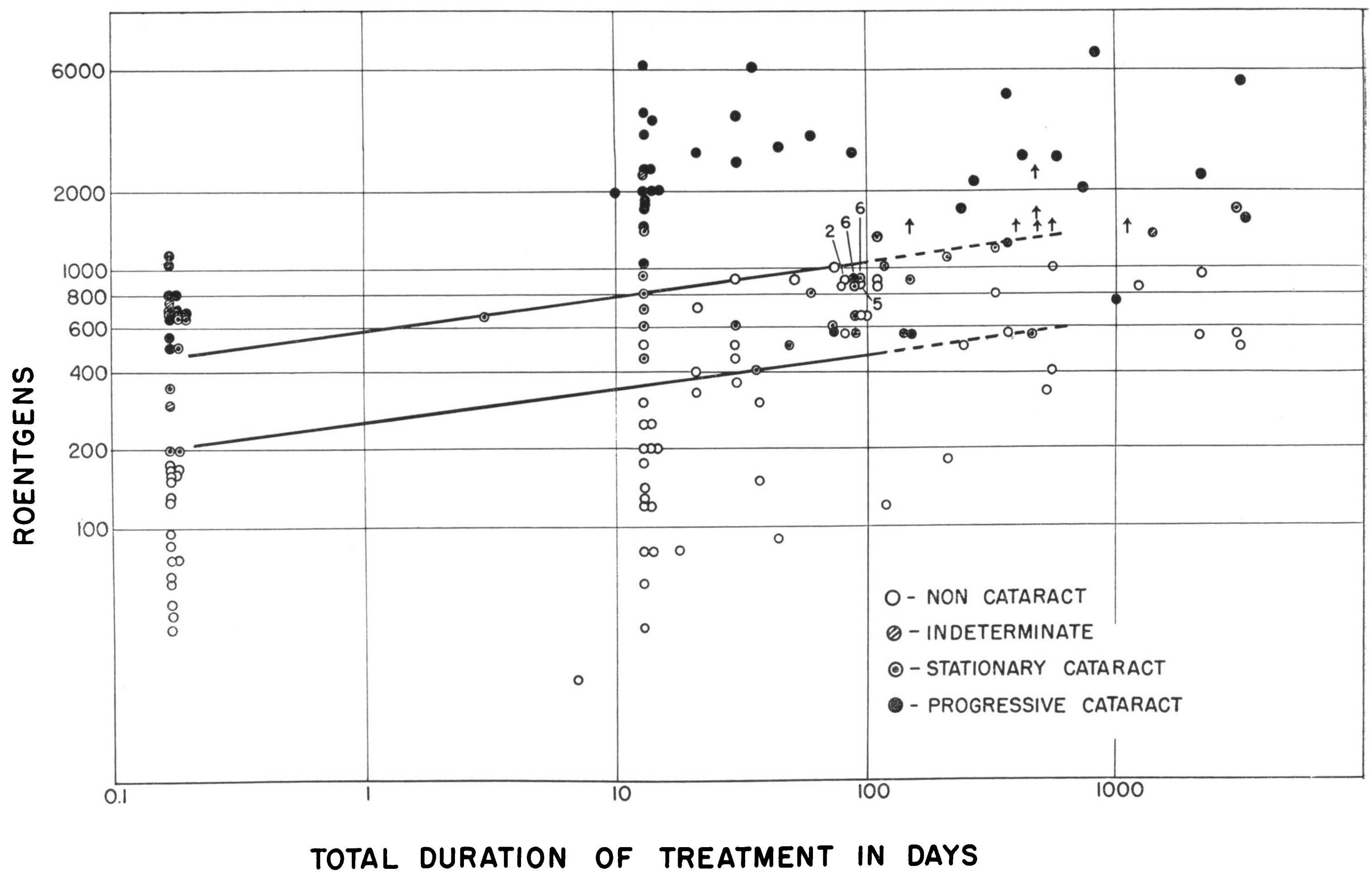
In the thesis presented to this society in 1956, the results of measurements of the dose of radiation to the lens in a series of patients were reported.[11] In this study there were 100 patients with proven radiation cataracts, and 73 patients who had received measurable amounts of radiation to the eye, but had not developed lens opacities, as evidenced by adequate eye examinations. In analyzing these data, the cases were grouped into three categories according to the duration of treatment—those who had received their treatment in a single dose, those with a treatment time of three weeks to three months, and those in whom treatment extended for more than three months. The doses in roentgens may be converted to rads by using a factor of from 0.93 to 0.97 for the qualities of radiation used. In the single treatment group the minimum cataractogenic dose found was 200 r. This dose resulted in a small, stationary opacity. In the group in which therapy was fractionated from three weeks to three months the minimum dose that resulted in a lens opacity was 400 r. With greater fractionation, over three months, the minimum cataractogenic dose was 550 r.

If the data were analyzed in another way—that is, by the maximum dose that did not produce lens opacities—a similar effect was found. Thus in the single treatment group the maximum non-cataractogenic dose was 200 r. In the cases with a treatment time of three weeks to three months, the highest dose that did not result in a cataract was 1000 r. When the duration of treatment was extended for more than three months, the maximum dose without cataracts was 1050 r.

These results seemed to suggest a time-dose relationship since a higher dose of radiation was necessary to produce a given effect, as the duration of treatment was increased. Conversely it might be said that the lens seemed able to tolerate higher doses of radiation with increased fractionation. The data for the cataract and non-cataract patients were plotted on a log-log scale, according to the method of Strandqvist. In the present work the single treatments were plotted at four hours, or 0.17 days, as an estimate of a "latent period." However, for present purposes the slope of the line obtained was changed very little if the time for a single treatment were taken as a few hours or even as one day. The cases treated with radon seeds alone were plotted at 13 days which was the time at which 90 per cent of the treatment was given. For the non-cataract patients, the log of dose was plotted against the log of the duration of treatment, and a line drawn at the upper limit of the points (Figure 1). The cataract cases were similarly plotted and a line drawn along their lower limit. Below the upper line were all of the non-cataracts, and above the lower line were all of the cataracts. In the zone between the lines were both cataracts and non-cataracts. The graph seemed to indicate a time-dose relationship. For a given dose delivered in a certain time, falling within the middle zone, a cataract might or might not be anticipated depending upon individual variations. Any time-dose relationship that fell within the upper zone would result in a lens opacity, and one that fell within the lower zone would not.

In these patients the times were the total, over-all durations of treatment. Within these intervals the fractionation was extremely variable. In general the longer the total treatment time the greater the variation in fractionation. Therefore Figure 1 should be used only as a general guide in estimating the possibility of a cataract from the time-dose factors. Also in this figure the progressive cataracts, which would seriously affect vision, are indicated separately.

The purpose of the experimental portion of this study was to check the validity of the clinical findings and determine whether or not there was an appreciable difference between single and divided doses of


6000
2000
1000
800
600
400
200
100
ROENTGENS
0.1
1
10
100
1000
TOTAL DURATION OF TREATMENT IN DAYS
2
6
6
5
NON CATARACT
INDETERMINATE
STATIONARY CATARACT
PROGRESSIVE CATARACT

X-radiation for the production of cataracts in the mammalian lens. The experiment was designed also to produce statistically significant data by using large enough groups of animals under controlled conditions.

EXPERIMENTAL STUDY

This series of experiments was started in 1958. Six-month-old female rats (White Sherman strain) were used. One eye of each animal was irradiated and the fellow eye used as a control. The animals were anesthetized with sodium nembutal and tied to a board. A small cone was used to limit the beam to one eye only as shown in Figure 2. In addition, the head was covered with a lead shield in which there was a small opening the size of the eye. The rest of the body of the animal was similarly shielded as further precaution against any leakage of radiation from the tube head. The dose to the eye was measured under experimental conditions with a phantom rat, using a small Baldwin-Farmer condenser ionization chamber.

In all of the experiments the following factors were used: 200 kvp—hvl 1.0 mm Cu.—tsd 20 cm. Single doses of 500 r, 1000 r, 1500 r, and 2000 r were given to each group which consisted of approximately 20 to 30 rats. The dose rate was 180 r per minute. Each animal was numbered individually by a coded ear punch and the treated eye could be either the right or the left.

Similar divided doses were delivered to one eye of each animal, in comparable groups, in a total of six days, given on the first, third, and sixth days. This time interval was chosen since, as a fraction of their life span, it approximates the human group with a treatment time of three weeks to three months. This is the duration of treatment most commonly employed clinically and hence constituted the largest clinical group.

Each of the approximately 250 animals was examined with the slit-lamp (corneal microscope) before treatment, and weekly, or every few weeks, thereafter. The examiner had no knowledge as to which eye had been treated, or, in most cases, which dosage group was being examined. At random times a whole group was re-examined on

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FIGURE 1

The logarithm of the dose for the cataract and non-cataract cases is shown plotted against the logarithm of the over-all treatment time. The numbers indicate several cases at one point. The vertical arrows are all progressive cataracts whose dose is higher than that indicated but could not be determined exactly. The indeterminate cases are those in which the classification of stationary or progressive could not be ascertained.

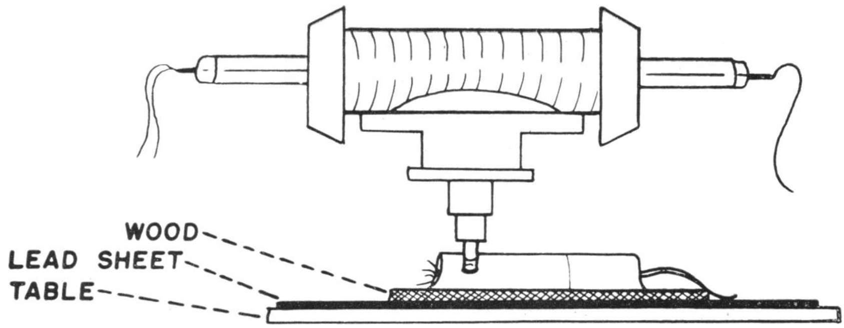

FIGURE 2

The experimental set-up in which only one eye is treated. The animal is covered with lead to shield it from any stray radiation.

the same day without the knowledge of the examiner. The two results so obtained showed no significant difference.

There were several ways in which the observations could have been scored. The method chosen was that using the average lens opacity at a given time of observation after exposure. The cataracts were graded 1+ to 4+ at each examination. In classifying the cataracts as 1, 2, 3, or 4+ the following criteria were used.

STAGE 1+

The earliest changes were an increase in the light reflex at the posterior pole of the lens, and clusters of vacuoles and opaque dots centrally in the posterior cortex and subcapsular region. A widening of the suture lines was observed quite frequently. With the higher doses, in many instances, there were tiny punctate opacities centrally or scattered throughout the mid-portion of the anterior capsule. These often appeared as soon as the posterior cortical changes. These early changes are shown in Figure 3.

STAGE 2+

These lenses showed a moderately dense posterior cortical opacity and some early opacifications of the anterior cortex (see Figure 4).

STAGE 3+

The posterior cortex was very opaque and the anterior cortex moderately so. The nucleus often showed beginning sclerosis. The general appearance of these lenses is shown in Figure 5.

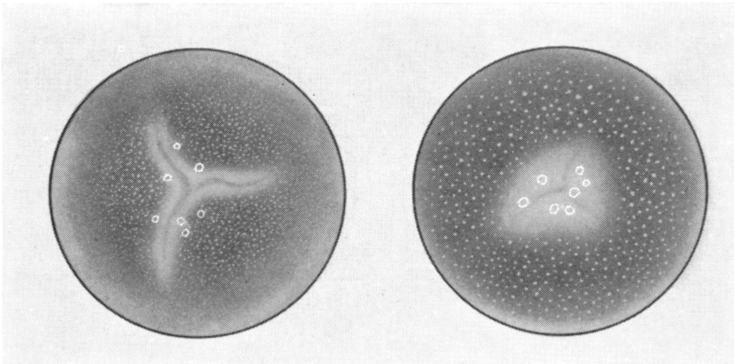

FIGURE 3

Two characteristic 1+ cataracts showing the early central posterior subcapsular vacuoles and dots with widening of the suture lines and an increase in the light reflex.

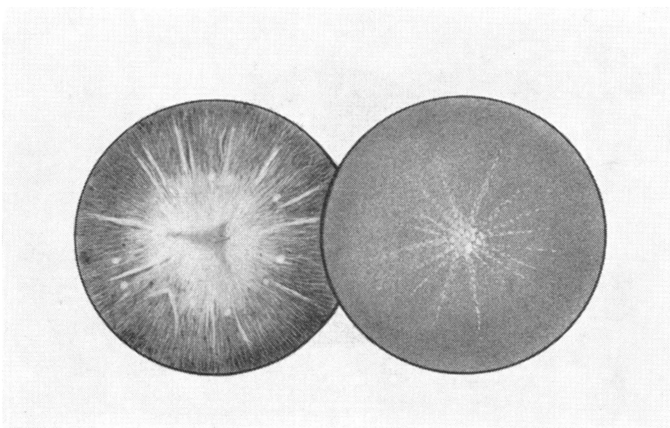

FIGURE 4

A 2+ cataract showing the increase in the posterior cortical opacity, left, and the beginning of the central anterior subcapsular opacity, right.

STAGE 4+

In this stage the lens was completely opaque, as illustrated in Figure 6.

After the rats were examined and the cataracts graded 1+ to 4+ the scores for each rat in a group were added and divided by the number of rats to give the average cataract. The plot could be made

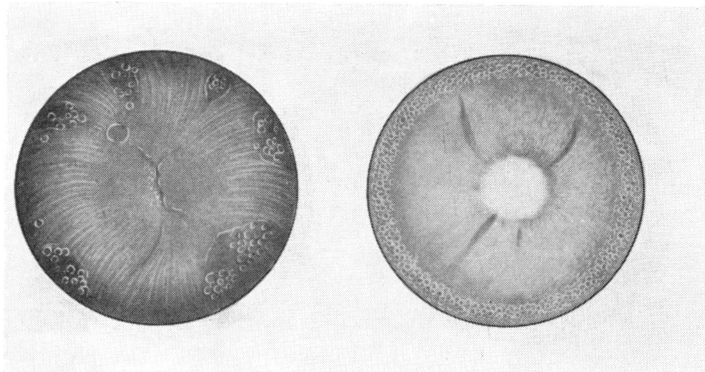

FIGURE 5
A stage 3+ opacity with extension of the changes in both the anterior and posterior cortex. The anterior cortical changes are on the left and the posterior cortical opacities are on the right.

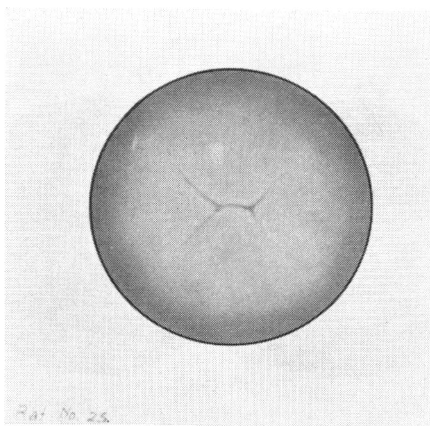

FIGURE 6
A stage 4+ cataract in which the lens is completely opaque.

in terms of per cents by defining an average of 4+ as 100 per cent. The percentages could be plotted against time. The method of plotting the score for each animal is shown in Figure 7 which is a condensation of the results of the examinations of one group.

This classification of the lens opacities as 1+ to 4+ is a clinical evaluation and not a quantitative measurement. Thus, while a 4+ opacity was definitely more severe or extensive than a 2+ cataract, SINGLE 1500r JANUARY 1960 200 Kvp

RAT NO.	JAN. 20	FEB 3		APR. 27	MAY 11	MAY 25	JUNE 8	JUNE 15	JULY 12	AUG. 3	AUG. 10	AUG. 24	SEPT. 14	OCT. 19
1R	0			DEAD										
2L	0			0	1+	1+	2+	2+	4+	4+	4+	4+	4+	4+
3R	0			0	1+	1+	1+	1+	2+	3+	3+	4+	4+	4+
4L	0			1+	0	1+	2+	2+	3+	3+	3+	4+	4+	4+
5R	0			0	1+	0	1+	1+	1+	2+	2+	2+	3+	4+
6L	0			1+	1+	1+	2+	1+	2+	4+	4+	4+	4+	4+
7R	0			1+	0	1+	1+	1+	2+	3+	3+	4+	4+	4+
30	0			0	0	1+	1+	2+	2+	3+	3+	4+	4+	4+
TOTAL	0			15	18	26	43	41	70	93	93	96	95	96
NO. OF RATS	29			25	25	25	25	25	25	25	25	25	24	24
TOTAL / NO. OF RATS = AV. CAT.				0.6	0.7	1.0	1.7	1.6	2.8	3.7	3.7	3.8	3.9	4.0
% CAT.				15	18	26	43	41	70	93	93	96	99	100
WEEKS AFTER RAD.	0.7			15	17	19	21	22	26	29	30	32	35	40

FIGURE 7

A portion of a work sheet for one experimental group showing the method of obtaining the average for the group from the cataract designation for each individual rat.

it cannot be assumed, without further evidence, that it was two times as severe. In fact, the statement "two times as severe" has no easily quantitatively measurable definition. However, for the purpose of comparison of the curves and the estimation of the relative effects, such semi-quantal responses were usable, especially since all of the data was similarly evaluated.

During the period of observation only a few of the control eyes developed senile opacities of varying degree toward the end of the experiment. These did not complicate the study,

RESULTS

2000 R—SINGLE AND DIVIDED

The eyes that received 2000 r of X-radiation in a single dose first showed lens opacities approximately nine weeks after treatment. The group reached an average of 2+ at 12 weeks and, by 19 weeks after exposure, all of the exposed eyes had dense (4+) cataracts (Figure 8).

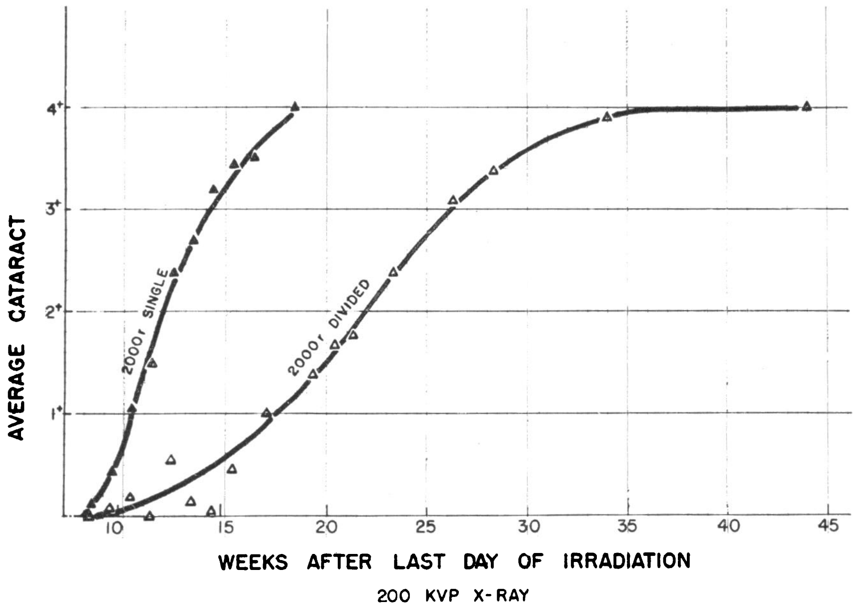

FIGURE 8

The curves obtained by plotting the average cataract for the 2000 r single and divided groups against the time elapsed after treatment.

The eyes exposed to 2000 r in three divided doses over a total period of six days were significantly different. The cataracts appeared somewhat more slowly and progressed to maturity at a considerably slower rate. The first, early opacities began to appear at about 12 weeks after treatment. At 22 weeks the average for the group was 2+. At about 40 weeks, all of the treated lenses showed 4+ changes (Figure 8).

1500 R—SINGLE AND DIVIDED

The experiment with a single dose of 1500 r of X-radiation was done twice with an interval of about one year. As can be seen from Figure 9 there was close agreement between them. The curve shown

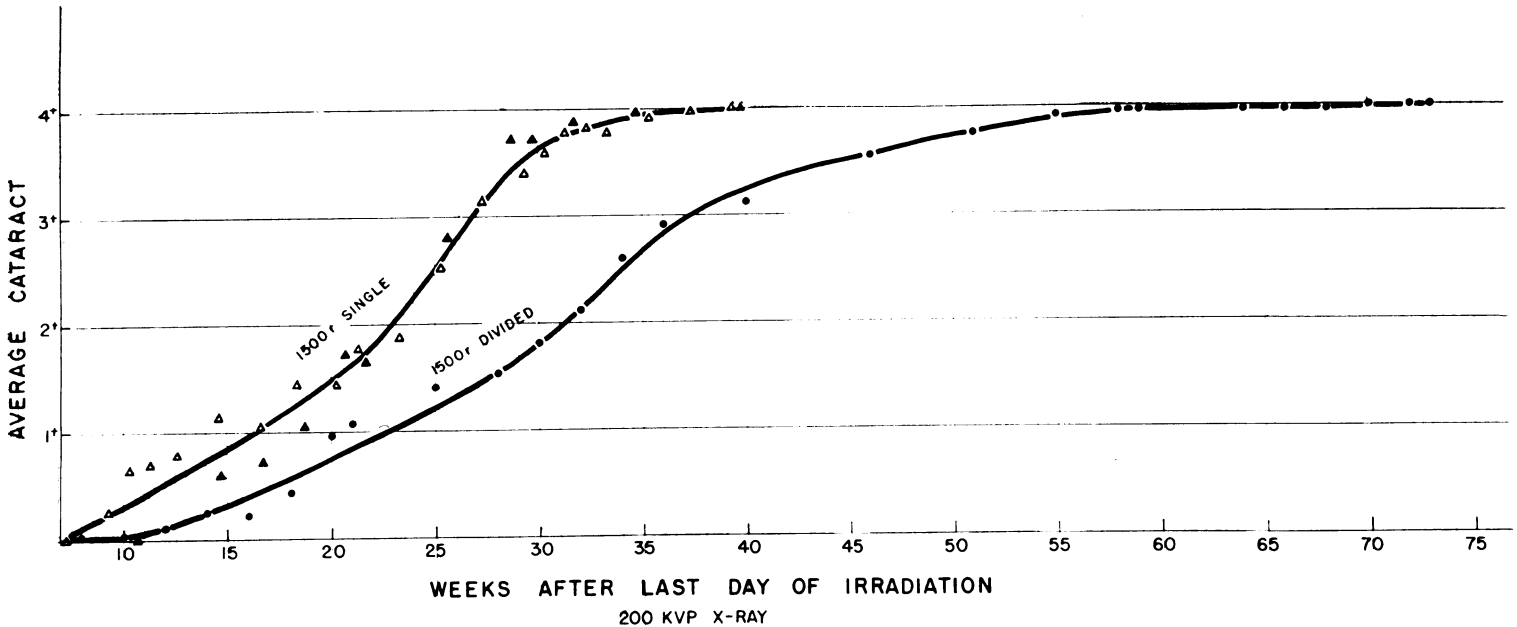

FIGURE 9

The curves for the 1500 r single and divided groups in which the average cataract is plotted against the time after treatment. The curve for the single treatment is the average of two experiments shown by the solid and open triangles.

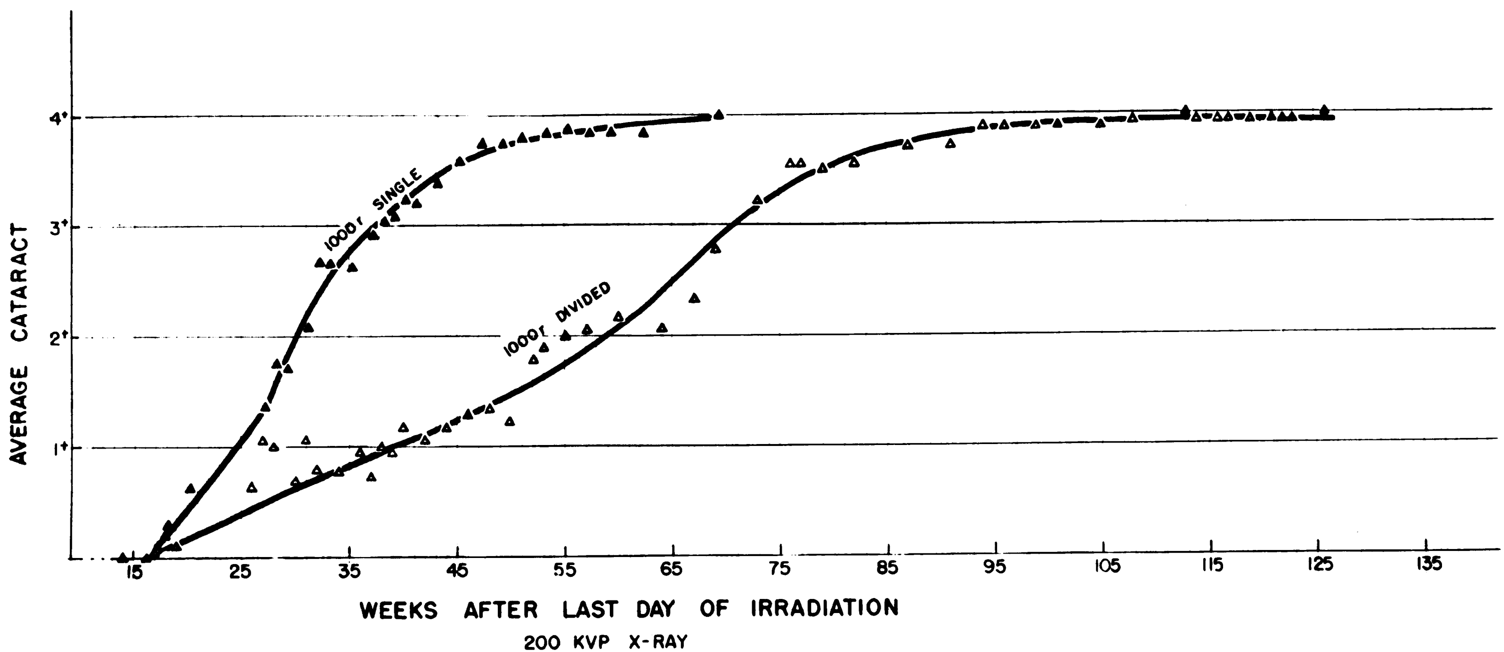

FIGURE 10

The curves for the 1000 r single and divided groups in which the average cataract is plotted against the time elapsed after treatment.

was the average of the two experiments. As will be discussed later, probit analysis showed no significant difference between the two experiments.

With a single dose of 1500 r of X-radiation, lens opacities were first observed about ten weeks after treatment, and at about 23 weeks the lenses were 2+. All of the exposed eyes showed 4+ cataracts at 40 weeks.

When this same dose was delivered in three treatments in six days the cataracts were first observed about ten weeks after exposure. At 31 weeks the average opacity was 2+ and by 70 weeks all of the lenses had become completely opaque (Figure 9).

1000 R—SINGLE AND DIVIDED

The eyes exposed to 1000 r of X-radiation in a single treatment showed early (1+) lens changes approximately 17 weeks after treatment. These progressed very slowly and reached 2+ in 31 weeks. By 70 weeks all of the lenses were 4+ (Figure 10).

When this same dose was delivered in three treatments over a total of six days, the first opacities were observed in 17 weeks. By 56 weeks the group had reached 2+, but required 110 weeks to become completely opaque (4+).

500 R—SINGLE AND DIVIDED

This group has been under observation for nearly 18 months and the end point has not been reached. In the single exposure group, lens changes were first noted at 22 weeks, as against 35 weeks for the divided group. The progression of the cataracts has been extremely slow. At 75 weeks, the average for the single group was 1.3+. The divided group has reached an average cataract of only 0.5 at 71 weeks (Figure 11).

ANALYSIS OF DATA

The experimental data for each group has been subjected to probit analysis* according to the method described by Finney.[12] The chi-square (χ^2) values were calculated in connection with the probit lines and indicated that there was good correspondence of the lines with the data. The number of weeks corresponding to a probit of five, or a 50 per cent incidence, which is a 2+ cataract in our notation, is

*This portion of the study was done with the assistance of Dr. Melvin Schwartz, Director, Division of Biometrics, Cornell Medical Center, New York City, New York.

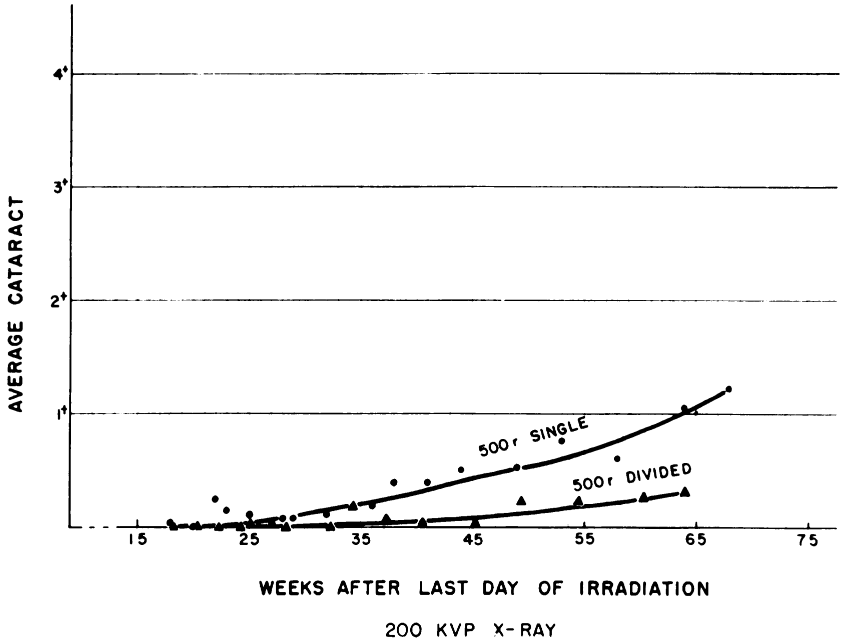

FIGURE 11

The 500 r single and divided curves in which the average cataract for each group is plotted against the time after exposure. Neither group has been followed sufficiently long to determine the final shape of each curve. However, a difference between them is apparent.

shown in Table 1 for each group of animals. One of the experiments was repeated as a test of the reproducibility of the results. The 1500 r single group was treated in 1959 and had a probit of five at 20.9 weeks, with 95 per cent fiducial limits from 19.7 to 22.1 weeks. Another group of the same dosage was redone in 1960 and gave a probit of five at 22.0 weeks, with fiducial limits from 20.9 to 23.1 weeks. Since these limits overlapped for the two groups, there was no significant difference between them. Thus these experimental results were reproducible.

TIME-DOSE RELATIONSHIP

In order to examine the relationship between single and divided doses of X-radiation some effect common to both must be used. The biological criterion defined for the "same effect" was taken to be the

TABLE 1. RESULTS OF PROBIT ANALYSIS

	2000r		*1500r (1959)*
	S	*D*	*S*
Weeks for 2^+ cat	12.3	22.0	20.9
Fiducial limits	11.7–13.0	20.8–23.4	19.7–22.1

	1500r (1960)		*1000r*	
	S	*D*	*S*	*D*
Weeks for 2^+ cat	22.0	29.9	31.1	55.4
Fiducial limits	20.9–23.1	28.2–31.6	29.6–32.6	52.9–57.9

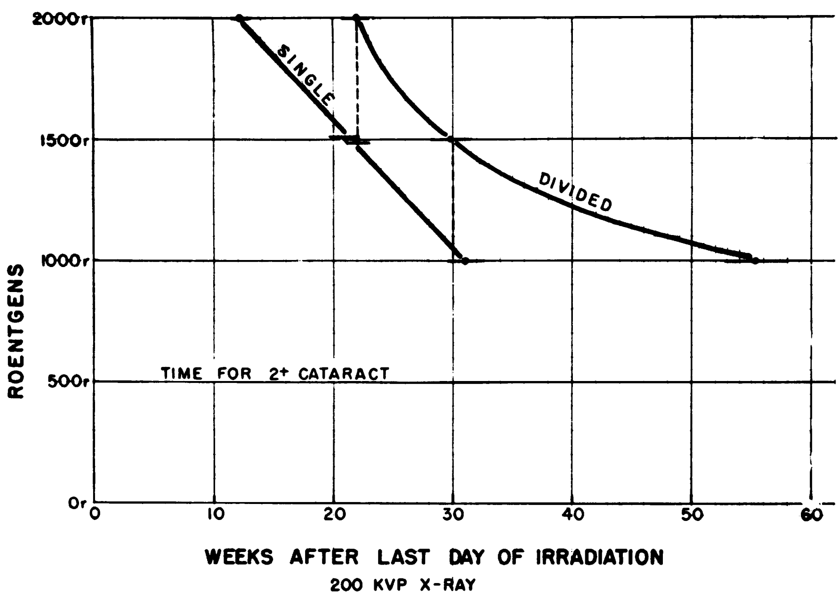

FIGURE 12

The time of onset of a 2+ cataract is plotted for a dose of 2000 r, 1500 r, and 1000 r, single and divided, from which iso-effect points can be determined. The fiducial limits are shown.

production of a 2+ cataract in the identical number of weeks. The data from Table 1 were plotted as shown in Figure 12. For instance, these data showed that a 2+ opacity appeared in 22.0 weeks for the 2000 r divided group, and the same effect occurred at the same time for a dose of 1480 r in a single exposure. These two points can be plotted as the log of the dose against the log of the over-all treatment time, as a Strandqvist type curve.

The single dose point was not considered as one day but four hours, as discussed above for Figure 2. The divided dose was plotted at the day of the last treatment. A line can then be drawn between these points showing the time-dose relationship for the production of cataracts.

Other pairs of points could be used which would give essentially the same slope. Thus, as can be seen on Figure 12, the 1500 r divided group developed a 2+ cataract in 30 weeks, and a plot of the single groups showed that 1050 r would produce a 2+ opacity in the same time. This was also plotted on a Strandquist type curve. The average of these two lines, which were very similar, was used to obtain the slope of the experimental curve.

In Figure 13 this experimental curve is shown compared with the slope for patients (Figure 1), and those for other tissues such as brain stem, skin, mycosis fungoides, cartilage, and squamous carcinoma as reported by DuSault.[2] The lower slope for the lens suggests that dividing the dose has less effect than it does for other tissues. However, the fact that there is a slope indicates that there is a time-dose relationship for the mammalian lens.

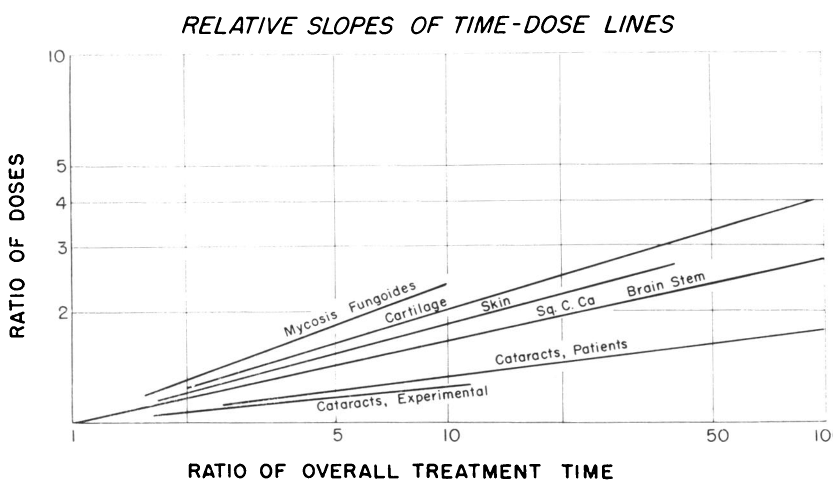

FIGURE 13

The average cataract time-dose curve obtained experimentally and for patients is shown compared to clinical studies of brain stem, skin, mycosis fungoides, cartilage, and squamous carcinoma. The lower slopes for the mammalian lens are apparent.

SUMMARY

In a previous clinical study of radiation cataracts the data suggested that a time-dose relationship existed for the production of lens opacities.

The doses in the clinical cases were plotted against the total duration of treatment which gave a time-dose relationship. This type of plotting gives an indication of the occurrence of a cataract for a certain dose delivered in a given time.

The experimental study was undertaken to determine, under controlled conditions, the relative effectiveness of single and divided doses of X-radiation on the mammalian lens. For the doses studied, a definite time-dose relationship was observed that gave a slope that might be expected when compared to known tissues. The experimental results also corroborated those found in the clinical study.

The same basic experimental X-ray curves will be used in the future for studies of the relative biologic effectiveness (RBE) of various qualities of radiation.

REFERENCES

1. Strandquist, M., Studien über die kumulative Wirkung der Röntgenstrahlen bei Fraktionierung, Acta radiol., Suppl. 55, 1944.
2. DuSault, L. A., Time-dose relationships, Am. J. Roentgenol., Radium Therapy and Nuclear Med., Vol. LXXV, 3:597, 1956.
3. DuSault, L. A., The time-dose relationship in radiotherapy, in Franz Buschke, ed., Progress in Radiotherapy. New York and London, Grune and Stratton, 1958, p. 100.
4. Leinfelder, P. J., Roentgen-ray cataract, Am. J. Ophth., 19:739, 1936.
5. Kandori, F., Studies on radiation cataract, Part I, Am. J. Ophth. 41:627, 1956.
6. Upton, A. C., K. W. Christenberry, *et al.*, The relative biologic effectiveness of neutrons, X-rays and gamma rays for the production of lens opacities, observations on mice, guinea pigs, and rabbits, Radiology, 67:686, 1956.
7. Riley, E. F., R. D. Richards, T. C. Evans, and P. J. Leinfelder, The effect of fractionating cataractogenic doses of neutrons and X-radiations, Radiat. Research, 7:446, 1957.
8. Evans, T. C., R. D. Richards, and E. F. Riley, Histologic studies of neutron and X-irradiated mouse lenses, Radiat. Research, 13:5, 737, 1960.
9. Adachi, T., and J. Horivchi, The effects of radiation on the hard tissues, the effect of radiation on the lens, Bull. Tokyo Med. Dent. Univ., 8:135, 1961.
10. Favre, M., and A. Zuppinger, Experimentelle Untersuchungen über die Strahlenkatarakte, Acta radiol. 186–190:81, 1959-60.
11. Merriam, G. R., Jr., A clinical study of radiation cataracts, Tr. Am. Ophth. Soc., 54:611, 1956.
12. Finney, D. J., Probit Analysis. Cambridge, England, At the University Press, 1947.

DISCUSSION

DR. P. J. LEINFELDER. The exact experimental work of Dr. Merriam confirms and quantitates observations that have been noted previously and which are referred to in his paper. I would like to add some similar as yet unpublished observations in which Dr. Riley, Dr. Richards, and I studied the effect of single and divided doses of X-rays and neutrons on the mouse lens. The graph shows the definite protection that resulted from the divided doses that were given during an interval of eight weeks. The effect of divided doses was less definite when high energy neutrons were used, and was essentially absent with intermediate energy neutrons.

Protection is also afforded by shielding part of the lens. If one fourth or more of the rabbit lens is shielded, doses as high as 12,000 r can be given without producing complete cataract. Actually opacities form in the radiated half of the lens, and then slowly regress. If alternate halves of the lens are similarly exposed with an interval of six or more weeks between the large doses complete cataract does not occur. It appears that with alternate radiations the first exposed half lens recovers sufficiently to protect the second irradiated half. It is our impression that the unexposed or recovered half of the lens takes over the necessary function of the lens while the irradiated portion is recovering from the ionization damage.

It is apparent that the dose-time relationship, and the radiation of part of the lens indicate a capacity of the lens epithelium, given time and opportunity, to recover to some extent from radiation injury, but the reason and mechanism of this is not known. I am interested in Dr. Merriam's ideas concerning this.

DR. MERRIAM. I wish to thank Dr. Leinfelder for his thoughtful and considered discussion. He and his group at Iowa City have done a great deal of excellent work in this field.

One of the purposes of our work was to see if reproducible basic curves could be developed which could be used in the future for the study of the relative biological effectiveness of various qualities of radiation. We are now engaged in a program of analyzing the relative effects of not only neutrons, but of protons on the lens. We hope eventually to be able to report some of this work.

As far as recovery is concerned, we have studiously avoided any mention of this, or any discussion of it. This is a whole subject in itself. How does tissue recover? What are the mechanisms involved? All we are prepared to say at this time is that there is a difference between single and divided doses of radiation on the lens. Whether this is truly recovery, as had been stated by many people, we are not yet prepared to say.